REMARKS

A check for the fee for a two month extension of time accompanies this response. Any fees that are due with this paper or application can be charged to Deposit Account No. 50-1213. If a Petition for extension of time is due, this paper can be considered such Petition.

Claims 1-21 are presently pending in this application. Claim 1 is amended to more distinctly claim the subject matter. Basis for the amendment can be found throughout the specification (for example, see page 9, line 27 through page 10, line 10; page 11, line 26 through page 12, line 6; and page 14, lines 15-27). For example, at page 11, line 27 through page 12, line 6, the specification states:

> Generally, when the immobilization attachment site is contained within the first primer region, the immobilization attachment remains intact under the selected cleavage conditions to retain a significant portion of nucleotides from the modified primer (e.g., those comprising the first primer region) in immobilized form. In accordance with the present method, the read length of the extension segment resulting from cleavage at the cleavable site is increased relative to the read length of the product composed of the primer and extension segment.

The instantly claimed primers are designed to improve the amount of new or useful information about a target DNA sequence by reducing the number of nucleotides contributed by the primer that appear in the resulting cleaved extension segment (page 30, lines 8-27). This amendment does not alter or limit the scope of the claims in any way but merely clarifies the subject matter encompassed by the claims. No new matter has been added.

A marked up copy per 37 C.F.R. §1.121 showing changes made to the claims is attached to this response.

INFORMATION DISCLOSURE STATEMENTS

The Office Action reports that references lined through were not considered because it is alleged that copies of the references listed in an Information Disclosure Statement mailed February 4, 2002, were not provided. A telephonic inquiry regarding this issue was made to Examiner Tung, who indicated that the boxes containing the references have since been located. The Examiner requested that applicant's representative submit a substitute copy of the PTO-1449 forms. The requested substitute copy is attached to this response. Examiner Tung is thanked for the courtesy extended in granting the telephonic interviews to confirm the status of the missing publications.

OBVIOUSNESS-TYPE DOUBLE PATENTING DOUBLE PATENTING REJECTION

Claims 1-21 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-19 of U.S. Patent No. 5,700,642 (hereinafter '642) and claims 15 and 17-18 of U.S. Patent No. 5,830,655 (hereinafter '655) because it is alleged that, although the conflicting claims are not identical, the instant claims are not patently distinct from the patent claims because claims 1-19 of patent '642 and claims 15 and 17-18 of patent '655 are directed to methods to determining the size of a primer extension product and use primers which allegedly have the same features as claimed in instant claims 1-21. In addition, the Examiner contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the instant application to claim the nucleic acid primer which has such features.

This rejection is respectfully traversed.

RELEVANT LAW

35 U.S.C. 121, third sentence, provides that where the Office requires restriction, the patent of either the parent or any divisional application thereof conforming to the requirement cannot be used as a reference against the other. See MPEP 806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Where restriction is required by the Office double patenting cannot be held, and thus, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP 804.01, which states:

> 35 U.S.C. 121 authorizes the Commissioner to restrict the claims in a patent application to a single invention when independent and distinct inventions are presented for examination. The third sentence of 35 U.S.C. 121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 U.S.C. 121 prohibition applies only where the Office has made a requirement for restriction. The prohibition does not apply where the divisional application was voluntarily filed by the applicant and not in response to an Office requirement for restriction. This apparent nullification of double patenting as a ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restrictions where the claims define essentially the same invention in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

ANALYSIS

A Restriction Requirement issued in an Office Action, mailed September 10, 1999, which divided the claimed subject matter into three groups:

I : claims 1-21 drawn to the primers as currently claimed;

II : claims 22-68 a kit and methods to determine the size of more than one primer extension product; and

III : claims 69-87 drawn to methods to determine the presence of a polymorphism.

An election was made and the requirement was made final. Group II includes the following independent claims:

54. A method for determining the size of more than one primer extension product, comprising:

(a) hybridizing a plurality of primers, each having a 5' end and a 3' end, with more than one target nucleic acid, wherein each of said primers

(i) is complementary to at least one target nucleic acid;
(ii) has a first region containing the 5′ end of the primer, and
(iii) has a second region, containing the 3′ end of the primer and a cleavable site, wherein the 3′ end is capable of being extended by an enzyme;

(b) extending the primers with the enzyme to generate a polynucleotide mixture containing more than one extension product;

(c) cleaving more than one extension product at its respective cleavable site to release more than one extension segment, wherein the location of the cleavable site of at least two primers is selected to increase the mass difference between their respective extension segments; and

(d) sizing the released extension segments by mass spectrometry, whereby said cleaving is effective to increase the read length of the extension segments relative to the read length of the products of step (b).

Group III includes the following method claim:

69. (Amended) A method of determining presence of a polymorphism, comprising:

(a) hybridizing a primer, having a 5′ end and a 3′ end, with a target nucleic acid suspected of containing a polymorphism, wherein said primer has a first region containing the 5′ end of the primer and a second region containing the 3′ end of the primer and a cleavable site;

(b) extending the 3′ end of the primer with a polymerase in the presence of a nucleotide to generate an extension product;

(c) cleaving said extension product at the cleavable site to release an extension segment;

(d) sizing the extension segment by mass spectrometry, whereby said cleaving is effective to increase the read length of the extension segment relative to the read length of the product of step (b); and

(e) identifying any added nucleotides.

Thus, the Office has stated that the instantly claimed primers are patently distinct from methods claims that employ the instantly claimed primers.

It is noted that the instant application is a continuation-in-part of Application Serial No. 08/639,363, filed April 26, 1996, now U.S. Patent 5,830,655, which is a continuation-in-part of Application Serial No. 08/445,751, filed May 22, 1995, now U.S. Patent 5,700,642.

Monforte '642

Monforte '642 independent claim 16 is directed to a:

> 1. A method for determining the size of a primer extension product, comprising
>
> (a) hybridizing a primer with a target nucleic acid, where said primer (i) is complementary to said target nucleic acid; (ii) has a first region containing the 5' end of the primer and an immobilization attachment site, and (iii) has a second region containing the 3' end of the primer, where the 3' end is capable of serving as a priming site for enzymatic extension and where said second region contains a selected cleavable site,
>
> (b) extending the primer enzymatically to generate a polynucleotide mixture containing an extension product composed of the primer and an extension segment;
>
> (c) cleaving said extension product at the cleavable site to release said extension segment, where prior to said cleaving the primer is immobilized at said immobilization attachment site; and
>
> (d) sizing the extension segment by mass spectrometry, whereby said cleaving is effective to increase the read length of the extension segment relative to the read length of the product of (b).
>
> 16. A method for determining the size of a primer extension product, comprising
>
> (a) combining first and second primers with a target nucleic acid under conditions that promote the hybridization of the primers to the nucleic acid, thus generating primer/nucleic acid complexes, where said first primer (i) is complementary to said target nucleic acid; (ii) has a first region containing the 5' end of the primer and an immobilization attachment site, and (iii) has a second region containing the 3' end of the primer, where the 3' end is capable of serving as a priming site for enzymatic extension and where said second region contains a cleavable site, and where said second primer is homologous to said target nucleic acid,
>
> (b) converting the primer/nucleic acid complexes to double-stranded fragments in the presence of a suitable polymerase and all four dNTPs,

> (c) amplifying the primer-containing fragments by successively repeating the steps of (i) denaturing the double-stranded fragments to produce single-strand fragments, (ii) hybridizing the single strands with the primers to form strand/primer complexes, (iii) generating double-stranded fragments from the strand/primer complexes in the presence of DNA polymerase and all four dNTPs, and (iv) repeating steps (i) to (iii) until a desired degree of amplification has been achieved,
> (d) denaturing the amplified fragments to generate a mixture including a product composed of the first primer and an extension segment;
> (e) immobilizing amplified fragments containing the first primer, utilizing said immobilization attachment site, and removing non-immobilized amplified fragments,
> (f) cleaving said immobilized fragments at the cleavable site to release the extension segment; and
> (g) sizing the extension segment by mass spectrometry, whereby said cleaving is effective to increase the read length of the extension segment relative to the read length of the product of (d).

Claims 1 and 16 of Montforte are directed to methods similar to claim 69, group II, of the instant application.

Monforte '655

Similarly, Monforte '655 contains claims directed to methods for determining the size of a primer extension product (independent claims 1, 15, and 16), to methods for determining a single base fingerprint of a target DNA sequence (independent claim 17), and to methods for determining an adenine fingerprint of a target DNA sequence (independent claim 18) that employ the primers. Hence Montforte '655 has claims that correspond to groups II and III in the instant application.

Conclusion

The Office has deemed the methods of groups II and III to be patentably distinct from the primers of group I, which were elected in this application. MPEP 806, paragraph 3 states that if restriction of subject matter is required by the Office, double patenting cannot be held. In this instance, restriction between claims to the primers and to methods using the primers has been required. Therefore, obviousness-type double patenting cannot be held.

THE REJECTION OF CLAIMS 1-9, 11-14, and 20-21 UNDER 35 U.S.C. §102(e)

Claims 1-9, 11-14, and 20-21 are rejected under 35 U.S.C. § 102(e) as anticipated by Köster *et al.* (U.S. Patent 5,622,824) because Köster *et al.* allegedly discloses a nucleic acid primer having a first region containing the 5' end of the primer and an immobilization attachment site, and a second region containing the 3' end of the primer and a chemically cleavable site, where the 3' end is capable of being extended by an enzyme. It is further alleged that the limitations of dependent claims 2-9, 11-14, and 20-21 are inherent in the disclosure of Köster *et al.* and thus the disclosure of Köster *et al.* allegedly "anticipates the limitations of claims 1-9, 11-14, and 20-21."

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S.. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Independent claim 1 and its dependent claims (2-21) are directed to a nucleic acid primer having a 5′ end and a 3′ end, which includes a first region containing the 5′ end of the primer and an immobilization attachment site; and a second region containing the 3′ end of the primer and a unique chemically cleavable site. The 3′ end is capable of being extended by an enzyme to generate an extension segment.

DIFFERENCES BETWEEN THE CLAIMS AND THE TEACHINGS OF THE CITED REFERENCE

Köster *et al.* (5,622,824)

Köster *et al.* discloses a method of determining the sequence of a nucleic acid by sequential directed cleavage of the nucleic acid by exonucleases and identification of the sequentially released fragments using mass spectrometry (MS). The reference discloses the use of MALDI-TOF MS for analysis of biomolecules, using PCR methods to amplify test material, and use of exonucleases and mass-modified nucleoside triphosphates to modify the sample biomolecule prior to analysis. Köster discloses attaching a linear single-stranded DNA fragment to a solid support via its 5′ end and attaching a target DNA to be sequenced via a "splint oligonucleotide" containing sequences complementary to the bound DNA fragment and the DNA fragment to be sequenced. Köster discloses releasing nucleotides from the 3′ end of the target DNA by contacting it with a 3′-exonuclease. As demonstrated below, Köster does not disclose primers where the 3′ end contains a chemically cleavable site, whereby, if the primer is immobilized, and the chemically cleavable site is cleaved, the remainder of the primer remains immobilized.

ANALYSIS

Instant claim 1 is directed to a nucleic acid primer having a 5′ end and a 3′ end, which includes a first region containing the 5′ end of the primer and an immobilization attachment site; and a second region containing the 3′ end of the primer and a chemically cleavable site. The cleavable site in the primer is such that, when the primer is immobilized, and the chemically cleavable site is cleaved,

the remainder of the primer remains immobilized (*i. e.*, the chemically cleavable site is a unique site). The 3′ end is capable of being extended by an enzyme to generate an extension segment. The primer can be depicted as:

—**ia**—5′———————————————————**cc**————3′—**enz**+ .

cc = a chemically cleavable site
ia = an immobilization attachment site **enz**+ = capability of being extended by an enzyme.

Köster discloses a linear single-stranded DNA fragment that can be attached to a solid support, such as via its 5′ end by covalent attachment to a functional group on the solid support. In some embodiments there is a spacer of sufficient length for a ligase to react; and a splint oligonucleotide with a sequence complementary in part to the solid bound oligonucleotide and to the 5′ end of a vector DNA to be sequenced (col. 7, line 62 - col. 8, line 15, and Figure 1). This can be depicted schematically as follows:

—**ia**—spacer-5′———————————————————3′ .

—— = a splint oligonucleotide
ia = an immobilization attachment site

Notably, Köster does not disclose a nucleic acid primer including a second region containing a unique chemical cleavage site. Köster does not disclose a nucleic acid primer containing a second region containing that includes the 3′ end of the primer, and a unique chemically cleavable site (*i.e.* a site, such that when the primer is immobilized via the 5′ immobilization attachment site, and the chemically cleavable site is cleaved, the remainder of the primer remains immobilized).

The Examiner contends that Köster discloses primers that contain chemically cleavable sites. Without addressing whether this reading of Köster is correct, Köster does not disclose or suggest including a unique chemically cleavable site (*i.e.*, a chemically cleavable site in the 3′ region of a primer, such that, when the primer is immobilized, upon cleavage only the 3′ portion that includes the site is removed).

Köster discloses incorporating exonucleotide resistant molecules containing chemically cleavable moieties such as alpha-thio dNTP groups throughout a nucleic acid molecule (col. 9, lines 30-42); but this embodiment includes a plurality of such moieties in the nucleic acid molecule. There is no disclosure or suggestion to introduce only a single occurrence of such groups in the 3' portion of the primer.

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. Köster does not disclose a nucleic acid primer having a second region at the 3' portion that includes a chemically cleavable site, whereby, when the primer is immobilized, and the chemically cleavable site is cleaved, the remainder of the primer remains immobilized. Thus, the cited reference fails to disclose every element of the claimed subject matter. Therefore, Köster does not anticipate any of claims 1-21.

THE REJECTION OF CLAIMS 15-19 UNDER 35 U.S.C. §103(a)

Claims 15-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Köster (U.S. Patent 5,622,824) in view of Köster (U.S. Patent 5,547,835) because Köster '824 allegedly teaches every element of the claimed subject matter except that the solid support includes a functionality selected from the group consisting of avidin and streptavidin, and antibody and anti-antibody, but the Examiner alleges that Köster '835 cures this defect.

The rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. App. 1980). Obviousness is tested by

"what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Under 35 U.S.C. §103, in order to set forth a case of *prima facie* obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. *See, e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963).

THE CLAIMS

Dependent claims 15-19 are directed to various embodiments of the primer of independent claim 1. For example, claim 15 is directed to a primer that includes a solid support, where the solid support includes a functionality selected from avidin and streptavidin. Claim 16 is directed to a primer that includes a solid support, where the solid support includes an antibody. Claim 17 depends from claim 16 and is directed to a primer where the antibody includes anti-digoxigenin. Claim 18 is directed to the primer of claim 1 where the immobilization attachment

site is a substituent on one of the bases or sugars of the primer. Claim 19 is directed to the primer of claim 1 where the immobilization attachment site is biotin or digoxigenin.

Differences between the cited references and the claimed subject matter

Köster (U.S. Patent 5,622,824)

See related section above (pages 13-14).

Köster (U.S. Patent 5,547,835)

Köster '835 is directed to a mass spectrometric method for sequencing using a Sanger sequencing strategy, in which one embodiment includes immobilizing the sequencing primers to a support using various linkers. Köster '835 teaches that the primer has a linking functionality L at the 5'-end that interacts with a suitable functionality L' on the solid support to form a reversible linkage L-L' (col. 11, lines 52-56). The linker chemistry can include biotin/streptavidin combinations as well as other enzymatic, chemical, or physical cleaving systems (col. 13, lines 17-35).

Köster '835 does not teach or suggest a nucleic acid primer having a second region that includes a unique chemically cleavable site. Thus, Köster '835 does not cure the deficiencies in the teachings of Köster '824.

ANALYSIS

The Office Action fails to establish that the claims are *prima facie* obvious for the following reasons.

The combination of teachings of Köster '824 with the teachings of Köster '835 does not result in the instantly claimed primers.

Claims 15-19 of the instant application are directed to various embodiments of the nucleic acid primer of claim 1. As discussed above, Köster '824 does not teach or suggest a nucleic acid primer that has a 5' and 3' portion that includes a unique chemically cleavable site. Köster '835 does not cure these defects. Köster '835 teaches a nucleic acid primer that has a 5' end containing a linking

functionality L, which can interact with a suitable functionality L' on a solid support to form a temporary reversible linkage, and a 3' end that is base-specifically terminated (col. 11, lines 52-56; Figure 1). This can be depicted as:

SS—L'–L—5'————————————————————3'—T.

Köster '835 does not teach or suggest a nucleic acid primer containing a second region containing the 3' end of the primer and a chemically cleavable site, such that when the primer is immobilized, and the chemically cleavable site is cleaved, the remainder of the primer remains immobilized. Instead, Köster '835 teaches a cleavable L—L' linkage at the 5' end of the nucleic acid primer, cleavage of which removes the entire primer from the solid support (column 11, line 52 - column 13, line 2).

Hence, Köster '835 fails to cure the deficiencies in the teachings of Köster '824. The combination of teachings of Köster '824 and Köster '835 fails to result in the instantly claimed primers. The combination of the teachings of Köster '824 and Köster '835 does not teach or suggest a nucleic acid primer having a 5' end and a 3' end, which includes a first region containing the 5' end of the primer and an immobilization attachment site; and a second region containing the 3' end of the primer and a unique chemically cleavable site and a 3' end that is capable of being extended by an enzyme to generate an extension segment. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness, and the rejection should be withdrawn.

THE REJECTION OF CLAIM 10 UNDER 35 U.S.C. §103(a)

As a preliminary matter, it is noted that the rejection of this claim cites to Köster 5,547,835 while the discussion within the rejection is directed to Köster 5,622,824. A telephonic conversation between applicant's representative and Examiner Tung on May 9, 2002 was held to clarify the grounds for rejection. The Examiner indicated during that conversation that the correct patent citation as grounds for rejection of claim 10 should be Köster 5,622,824. Examiner Tung is

thanked for the courtesy extended in granting the telephonic interview to clarify this issue.

Claim 10 is rejected under 35 U.S.C. §103(a) as being unpatentable over Köster (U.S. Patent 5,662,824) in view of Richards *et al.* (U.S. Patent 5,427,929) because Köster allegedly teaches every element of claims 1-9, 11-14, and 20-21, and although Köster does not teach the ligase enzyme of claim 10, the Examiner alleges that Richards *et al.* cures this defect.

The rejection is respectfully traversed.

RELEVANT LAW

See related section above (pages 18-19).

THE CLAIMS

Claim 10 depends from claim 1 and is directed to the primer of claim 1, where the enzyme extending the 3′ end is a ligase.

Differences between the cited references and the claimed subject matter

Köster (U.S. Patent 5,622,824)

See related section above (pages 13-14). In addition, Köster *et al.* does not teach or suggest using ligase for extending the primer at the 3′ end.

Richards *et al.* (U.S. Patent 5,427,929)

Richards *et al.* teaches a method for reducing carryover contamination in an amplification procedure by incorporating at least one modification into the amplification product to distinguish it from the target sequence and allow it to be identified as background contamination. The reference teaches including restriction endonuclease target sites as cleavable sites in the amplification products, and use of restriction endonucleases to cleave the resulting modified products (see, e.g., Figures 5-9, 12-15, and 19). Prior to further amplification, the sample is treated to selectively cleave the contaminant amplification product so that it cannot be amplified in the new sample. The reference teaches a method of using ribonucleotide substitution at the 3′-end of an amplification product and then extending it using PCR or LCR so that the ribonucleotide substitution is internalized

in the sequence (col. 17, lines 33-45 and line 65 through col. 18, line 13). Richards *et al.* teaches that it is preferred to locate the chemically cleavable site modification near the middle of an amplification probe or primer so that disruption of hybridization will be minimized (col. 17, lines 19-22). Richards *et al.* teaches the introduction of a number of different types of modifications into the amplification product (col. 9, lines 24-27) and the number of modification sites incorporated into the amplification product may vary (col. 10, lines 7-10). Richards *et al.* teaches that the amplification product can be modified at or about any location other than the extending end of the primer that does not interfere with amplification, and in that case the modification should be modified at its 5' end (col. 11, lines 15-30).

Richards *et al.* does not teach or suggest a nucleic acid primer containing a second region containing the 3' end of the primer and a unique a chemically cleavable site.

ANALYSIS

(1) There would have been no motivation to have combined the teachings of Köster *et al.* with those of Richards *et al.*

The Examiner contends that one of ordinary skill in the art at the time of the instant application would have been motivated to "use a ligase in a nucleic acid polymerization reaction as taught by Richards *et al.* because the method of Richards *et al.* is efficient and economy [*sic*] for reducing carryover contamination in an amplification procedure" (citing the Abstract).

It is unclear what the Examiner is alleging is the motivation to combine these references. Richards *et al.* teaches a method for reducing carryover contamination in an amplification procedure, a problem that is not present in either the instant application or the teachings of Köster *et al.* Richards *et al.* utilizes electrophoresis, radiolabeling and autoradiography for detection of the amplification products, where background contamination presents a significant problem. Both Köster *et al.* and the instant application utilize mass spectrometry for analysis, where generation of smaller fragmentation products of undesired amplification products by the method of Richards *et al.* would present more of a problem then the intact amplification

product itself (Köster *et al.* '835, col. 6, lines 6-65). Therefore there would have been no motivation to combine the teachings of these references. No motivation existed, outside of Applicants' teachings, to reduce the length of a nucleic acid by cleaving at a 3'-region cleavage site prior to mass spectrometric analysis.

(2) Notwithstanding the lack of motivation, the combination of teachings of Köster *et al.* with the teachings of Richards *et al.* does not result in the instantly claimed nucleic acid primers.

The combination of Köster *et al.* and Richards *et al.* does not result in the instantly claimed subject matter. The Office Action alleges that Köster *et al.* teaches every element of the instantly claimed primer except the use of a ligase to extend the primer, but contends that Richards *et al.* cures this defect because Richards *et al.* teaches a primer with a 3'-end cleavable site and a method that involves a ligase chain reaction.

As discussed above, Köster '824 does not disclose a nucleic acid primer containing a second region containing the 3' end of the primer and a unique chemically cleavable site, whereby, when the primer is immobilized, and the chemically cleavable site is cleaved, the remainder of the primer remains immobilized.

Richards *et al.* does not cure this defect. Richards *et al.* teaches the placement of chemically cleavable sites in primers near the center of the probes (see Figures 5-9 and col. 17, lines 19-22), and where the cleavage is accomplished by use of restriction enzymes, the reference teaches that placing the enzyme recognition site as centrally as possible is preferred (col. 13, lines 10-13). The Examiner alleges that Richards *et al.* teaches incorporating a chemical cleavage site at the 3'-end of a primer (col. 16 line 65 through col. 17, line 5). Richards *et al.* actually teaches modification at the 5'-end of one partial probe and the 3'-end of another partial probe, and subsequently joining the partial probes such that the chemically cleavable modification site is near the middle of amplification probe or primer in order to minimize disruption of hybridization (col. 17, lines 19-22; and, e.g., Figure 10) or partial priming (column 15, lines 51-68). Therefore Richards *et*

al. does not teach or suggest that the chemical cleavage site is in the 3' portion of the primer, but instead, that the chemical cleavage site of the primer is near the middle of the amplification probe or primer.

Richards *et al.* does not teach or suggest a unique chemically cleavable site in the 3' portion of a primer, whereby, when the primer is immobilized, and the chemically cleavable site is cleaved, the remainder of the primer remains immobilized. Richards *et al.* teaches that multiple modification sites may be incorporated into the amplification product (col. 10, lines 7-10), and that the amplification product can be modified at any location other than the extending end of the primer (col. 11, lines 15-30).

Further, Richards *et al.* does not teach or suggest modification of the 3'-region of a primer in order to allow selective cleavage of the extension segment from the primer, whereby, when the primer is immobilized, and the chemically cleavable site is cleaved, the remainder of the primer remains immobilized. Instead, Richards *et al.* teaches the incorporation of chemical cleavage sites in order to destroy the modified amplification product by treatment with reagent that cleaves the modification site (col, 4, lines 1-10; col. 15, lines 39-68; and col. 16, 51-55).

The combination of the teachings of Köster *et al.* and Richards *et al.* does not result in the subject matter of the pending claims. Neither reference, singly or in combination, teaches or suggests a nucleic acid primer having a second region containing the 3' portion of the primer capable of being extended by an enzyme to generate an extension segment, nor a nucleic acid primer containing a second region containing the 3' portion of the primer and a unique chemically cleavable site.

Therefore, because the combination of teachings of the references does not result in the instantly claimed nucleic acid primers, the Examiner has failed to set forth a *prima facie* case of obviousness. The Applicants respectfully request that the rejection be withdrawn.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Monforte *et al.*

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For: *PRIMERS USEFUL FOR SIZING NUCLEIC ACIDS*

Art Unit: 1637

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Alicia Bradbury

MARKED UP CLAIMS IN ACCORDANCE WITH 37 C.F.R. § 1.121

Please amend claim 1 as follows:

1. (Amended) A nucleic acid primer having a 5′ end and a 3′ end, comprising:

(a) a first region containing the 5′ end of the primer and an immobilization attachment site; and

(b) a second region containing the 3′ end of the primer, wherein the 3′ end is capable of being extended by an enzyme to generate an extension segment, and a chemically cleavable site, [wherein the 3′ end is capable of being extended by an enzyme]

whereby, when the primer is immobilized via the immobilization attachment site, and the chemically cleavable site is cleaved, the remainder of the primer remains immobilized.